REMARKS

Claim Amendments

Claim 20 has been amended to delete reference to treating tumor growth. Claim 23 has been cancelled. These amendments render moot the reasons the rejections of claim 20 and 23 under 35 U.S.C. §112, first and second paragraphs, set forth on page 2 of the office action.

Claim 31 has been added to define the treatment of tumor growth mediated by raf kinase which was cancelled with the amendment to claim 20. Support for new claim 31 in specifying raf mediated tumors is found on pages 1 and 2 which discusses prior investigations by Monia et al. (cited in the specification) into the inhibition of raf for treating a variety of tumor types. The specification clearly discloses the claimed compounds are effective in inhibiting raf kinase. Based on the state of the art with respect to the correlation of the inhibition of raf kinase with the inhibition of growth of a variety of tumor types, and the raf activity the compounds of claim 1, new claim 31 is clearly enabled.

There is no evidence of record to refute the findings or conclusions made by Monia et al.(cited in the specification) or that any compounds of claim 1 herein, as inhibitors of raf kinase, would not be effective in treating solid tumors mediated by raf. The specification provides ample guidance as to how to prepare pharmaceutical compositions with the compounds of claim 1 and how to administer these compositions in the treatment of cancers. See, e.g., pages 30-40. The specification also provides dosage ranges for the various methods of administration (see pages 43-44). Given the extent of the disclosure provided, it would at most involve routine experimentation if any at all, for one of ordinary skill in the art to treat raf mediated solid tumors with a compound of this invention. This is clearly sufficient to satisfy the statute. See *Amgen v Hoechst Marion Roussel*, 314 F.2d 1313, 65 USPQ2d 1385 (Fed. Cir. 2003). Using the claimed compounds would be routine for those of ordinary skill in the art in view of applicant's disclosure.

The examiner cited Wands to support the rejection of claims 20 and 23. It is noted the discussion in Wands includes the statement, "considerable amount of experimentation is permissible, if it is merely routine, or if the specification in

question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

Applicants also wish to point out the specification provides more than adequate guidance to enable the methods of claim 31 in that an in vitro biochemical raf kinase assay is provided on pages128-129 to determine percent inhibition of c-raf kinase. One of ordinary skill in the art by performing the same or similar tests, can, by routine experimentation, determine the activity levels of each of the compounds of claim 1 in inhibiting raf kinase , which has been correlated with the treatment of various tumors. This is absolutely routine in the field.

Rejection of claims 1-13, 15-17, 20, 22, 24-30 under 35 U.S.C.§112, first paragraph

Applicants maintain that there is no basis for the rejection of claims 1-13, 15-17, 20, 22, 24-30 under 35 U.S.C.§112, and that one skilled in the art could make and use the compounds defined therein based on the disclosure within the specification.

Applicants traverse the rejection of all pending claims (claims 1-13, 15-17, 20, 22, 24-30) under 35 U.S.C. §112, first paragraph, based on the allegation that the specification is not enabling for compounds of formula I where B is naphthyl or pyridinyl. It is further alleged that it would be undue experimentation to synthesize these compounds and then subject these compounds to Applicants raf-1 biochemical assay.

The compounds of claims 1-13, 15-17, 20, 22, 24-30 are clearly defined in the specification. No evidence has been presented or allegations made that the compounds claimed are not clearly defined. With the structure of the claimed compounds clearly defined by formula I, one of ordinary skill in art could synthesize these compounds without undue experimentation relying only on conventional methods for synthesizing ureas known in the art such as those disclosed on page 27 of the application.

In addition to the conventional methods, the specification provides ample guidance to one skilled in the art as to how to prepare the claimed compounds. General preparative methods for synthesizing ureas are given on pages 21-26. One

skilled in the art would recognize the appropriate starting materials (substituted anilines and substituted nitro-aryls) necessary to employ in these methods to arrive at the claimed compounds. Methods for preparing the starting materials are well known (substituted anilines and substituted nitro-aryls) and publications, which describe such methods, are disclosed on page 24 of the specification and incorporated by reference. Additional guidance on the selection of starting materials and reaction conditions is provided by the specific preparations of the citations provided on page 27 and further guidance is provided by the disclosure and examples that appear are pages 51-127. Based on the disclosure within the specification and conventional methods known in the art, one of ordinary skill in the art clearly would be able to prepare the claimed compounds without undue experimentation. No evidence has been presented to the contrary.

As to using the compounds of claims 1-13, 15-17, 20, 22, 24-30, the specification clearly discloses that the compounds have pharmacological activity based on the disclosure on page 1, lines 10-14; page 10, lines 3-13, pages 30-45; and assays disclosed on pages 127-129. The compounds are said to be effective in treating hyper-proliferative disorders, examples of which are given on pages 41-43.

The specification provides ample guidance on how to use the claimed compounds in treating these various conditions. Disclosure is provided on how to prepare pharmaceutical compositions with the compounds of this invention, including dosage ranges, and how to administer these compositions in the treatment of various conditions is provided on pages 30-45. The specification also provides assays for determining the activity levels of the compounds on pages 127-129. One of ordinary skill in the art by performing the same assays described in the specification or similar tests, can, by routine experimentation, determine the activity levels of each of the claimed compounds in treating the various conditions known in the art to be correlated with raf inhibition. Given the extent of the disclosure provided, it would at most involve routine experimentation, if any at all, for one of ordinary skill in the art to make and use the compounds of claims 1-13, 15-17, 20, 22, 24-30 in treating various conditions such as cancer and other hyperproliferative disorders mediated by raf kinase.

Applicants submit methods for synthesizing compounds of formula I where B is naphthyl or pyridinyl and testing these compounds with Applicants' raf-1 biochemical assay are sufficiently described in the specification and the performance of these methods would be routine. Synthesis of a compound where B is naphthyl or pyridinyl would simply require the appropriate selection of starting materials for the synthesis procedures described in the specification. Related ureas having naphthyl or pyridinyl groups bound directly to the urea group are known in the art and disclosed in WO 99/32436 and WO 99/32106, cited on page 27 of the specification. WO 99/32116 discloses about 30 compounds where pyridinyl is bound directly to the urea group (See examples 14, 16, 24, 46, 49, 50, 161-163, 166, 172, 198, 199, 201, 202-205, 208, 220, 222-227, 233, 236, 259, 276, 293, 353-357) and WO 99/32436 provides 12 compounds where naphthyl is bound to directly to the urea group (see examples 28 and 120-130). Similarly, the following publications and patents describe methods for preparing ureas where "B" is naphthyl: WO 00/55152, WO 00/55139, WO 02/083628, U.S. 6,297,381 and U.S. 6,525,046. The synthesis procedures described in the specification are similar to those described in WO 99/32436 and WO 99/32106, which are incorporated by reference in the subject application. The prior art syntheses of ureas where B is naphthyl or pyridinyl using similar methods to those disclosed in the specification is evidence that the specification provides sufficient disclosure for one skilled in the art to synthesize compounds of formula I where B is naphthyl or pyridinyl without undue experimentation.

The Examiner notes that the compounds illustrated in the copending applications have distinct moieties (isoxazoles) for "A". As disclosed in the specification, the compounds of this invention can be synthesized in a number of ways including reacting an amine group on moiety "B" with a carbonyl group on moiety "A" to form a urea. It would be routine for one skilled in the art to incorporate a moiety "A" consistent with this invention in a urea compound instead of an isoxazole by selecting the appropriate starting materials.

The Applicants have provided effective assays and details to perform them to assess the raf inhibiting activity of these compounds. No evidence has been presented to the contrary. In fact, the examples identified in WO 99/32436 and WO 99/32106 and other published applications illustrate that urea compounds where pyridinyl or

naphthyl are bound directly to the urea group can be effective inhibitors of raf using assays similar to the assay described in the subject application. The use of similar assay to asses the activity of similar ureas is evidence the use of the assays described in the specification would be routine. Therefore, to test the compounds of Formula I including those where B is pyridinyl or naphthyl for raf inhibition would be routine.

In that analogous compounds with pyridinyl or naphthyl structures corresponding to moiety "B" have been shown to be effective kinase inhibitors, there is no basis to support the allegation that any compounds of formula I herein are ineffective and not enabled. The disclosures within WO 99/32106 and WO 99/2106 and other publications rebut the Examiner's assumption that the pyridinyl moiety will negatively impact raf kinase inhibition. These disclosures provide a reasonable basis to conclude that compounds where "B" is pyridinyl or naphthyl will share the same biological properties as compounds where "B" is phenyl.

The examiner has measured the extent of experimentation by the number of the compounds encompassed by formula I. The scope of a claim is not the proper test as to whether undue experimentation is necessary to practice the subject matter therein. The synthesis and testing of the full scope of compounds within the scope of formula I will require significant repetition. Such repetition is routine and not undue experimentation.

The examiner alleges evidence has been presented to support the rejection. Reference is made to the unpredictability of receptor binding and the allegedly different chemical characteristics between a pyridinyl ring and a quinolinyl ring, naphthyl ring, or phenyl ring in that the pyridinyl ring is π-electron deficient and a strongly basic hydrogen bond acceptor.

It is alleged one skilled in the art would question the inclusion of such diverse rings based on this evidence but no citation has been offered to demonstrate one skilled in the art would express such doubt, particularly in that many publications, including WO 99/32436 and WO 99/32106, teach that urea compounds having a naphthyl or pyridinyl moiety corresponding to B of formula I does not destroy the raf kinase inhibiting activity of the urea compound.

No evidence has been presented that the distinctions in the electron configuration of the pyridine ring will impact properties of compounds such as formula I which have more than one two cyclic moieties and a urea group. Applicants have shown that other variations in structure of the compounds of formula I do not destroy raf kinase inhibitory activity of the ureas of formula I, although some variation in activity does occur. Based on this showing and the disclosure within the prior art, a skilled artisan would have no basis to doubt any of the compounds of formula I would be effective in inhibiting raf kinase. The examiner cites no teaching which would lead a skilled artisan away from using analogous urea compounds where B is naphthyl or pyridinyl.

For the reasons stated above, Applicants maintain that they have provide more than adequate guidance to enable the claimed invention and submit all claims meet the requirements of 35 U.S.C. §112, first paragraph.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

/Richard J. Traverso/

Richard J. Traverso, Reg. No. 30,595
Attorney/Agent for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410
Attorney Docket No.: BAYER-0044
Date: January 21, 2009